shown in our patient's blood smear, may be responsible for the increase of red-cell osmotic fragility.

In our case, the infant demonstrated all typical features of hemolytic disease of the newborn due to anti-M. The family was warned for future pregnancies.

In cases of hemolytic disease of the newborn of unusual or unknown etiology, showing negative direct antiglobulin tests and marked increase of red-cell fragility, and in cases of hydrops fetalis and intrauterine death, anti-M must definitely be considered.

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## Elevated Serum CA 125 Tumor Marker in Chronic Lymphocytic Leukemia With Mesothelial Involvement

*To the Editor:* Cancer antigen 125 (CA 125) is a tumor marker detected in the serum samples of about 80% of patients with ovarian cancer. It is used primarily to monitor treatment response and to detect early recurrence. Recently, increased levels in some cases of lymphoid malignances have been reported [1], mainly in non-Hodgkin's lymphomas (NHL) with abdominal involvement. We present the case of a patient with a chronic lymphocytic leukemia (CLL) with mesothelial involvement and elevated CA 125 serum levels.

An 82-year-old woman presented with a 4-week history of weight loss, malaise, and dyspnea. On physical examination she was cachectic, with splenomegaly of 8 cm and decreased breathing sounds in the left lung. Lymphadenopathy or hepatomegaly were not found. Her abdomen was distended and tympanic. Radiographic examination showed left pleural effusion. Laboratory tests revealed Hb of 149g/l, MCV of 93 fl, platelet count of 179 $\times$ $10^9$/l, WBC count of 14.9 $\times$ $10^9$/l with bands 2%, neutrophils 33%, lymphocytes 35%, prolymphocytes 25%, monocytes 4%, eosinophils 1%, and basophils 0%), ESR of 5 mm/hr, LDH of 589 U/l (normal, 230–460 U/l), and CA 125 of 928 U/ml (normal, $< 35$). Carcinoembryonic antigen (CEA) and $\alpha$-fetoprotein levels were normal. Ultrasound abdominal examination and computed axial tomographic scan showed splenomegaly with pleural and peritoneal effusion. The ovaries, pancreas, and bowel were normal. Cytological examination of pleural effusion, as well as peripheral blood and bone marrow, demonstrated the presence of a clonal proliferation of well-differentiated lymphocytes with 15–25% prolymphocytes. Immunocytological findings agreed with the diagnosis of mixed-cell type CLL. Cytogenetic analysis did not shown karyotype abnormalities, but using in situ hybridization techniques, 12 trisomy was found.

A diagnosis of chronic lymphocytic leukemia/prolymphocytic leukemia (CLL/PL) was made, and chlorambucil treatment was started. The patient's condition gradually deteriorated, the evolutive level of CA 125 increased (in the last determination, CA 125 was 1,367 U/ml), and she died 5 months after admission.

CA 125 tumor-associated antigen is a glycoprotein recognized by a monoclonal antibody (OC-125) raised against a human epithelial ovarian-cancer cell line. The relationship of CA 125 to hematologic diseases has recently been reported [1,2]. However, the biological significance of elevated CA 125 levels in this setting remains unclear. In fact, a variety of hematopoietic and lymphoreticular tissues have not shown immunoreactivity for this antigen. Zeillemaker et al. [3] investigated the secretion of this tumor marker using cultured human mesothelial cells. They concluded that there is a constitutive production of this glycoprotein from mesothelial cells, and that its secretion can be enhanced by some inflammatory cytokines. Apel and Fernandes [4] support the hypothesis that different organs and structures of mesothelial origin produce this glycoprotein in response to disease. Thus, it appears that his biological marker would indicate an extra nodal spread, especially pleural or peritoneal involvement. Pabst and Ludwig [5] reported increased CA 125 levels in 10 patients with NHL and in 1 patient with CLL with abdominal lymphadenopathy. They proposed that CA 125 is produced by mesothelial cells in response to lymphokine released by the NHL cells. We agree with this hypothesis; in our case, as in all the above-mentioned cases, increased serum CA 125 concentration was present without evidence of ovarian cancer, but with an extensive involvement of serous cavities. High serum level of CA 125 in CLL is absolutely exceptional (in our review we found only one such patient) [5]. This is the second case that has been reported, and we suppose that the pathophysiology of this finding is similar to that of NHL. Further investigations and sequential analysis of CA 125 levels are necessary to delineate its role as a prognostic factor in NHL and its applications as an earlier marker of lymphoproliferative disease with abdominal and/or extranodal spread.

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## Pulsed Dexamethasone for Refractory Idiopathic Thrombocytopenic Purpura

*To the Editor:* A majority of patients with idiopathic thrombocytopenic purpura (ITP) can be successfully managed with corticosteroids and splenectomy, although relapses are common. Patients who are refractory to

**TABLE I. Characteristics of Patients Before Initiation of Pulsed Dexamethasone for Idiopathic Thrombocytopenic Purpura***

| Patient | Age/sex | Duration of ITP (months) | Prior therapy before DXM | Platelet count ($\times 10^9$/l) before first DXM pulse |
|---|---|---|---|---|
| 1 | 30/F | 17 | Prednisolone[a]<br>Splenectomy[a] | 9 |
| 2 | 22/F | 23 | Prednisolone[b]<br>IVG,[a] splenectomy[a]<br>Azathioprim,[a] VCR[b]<br>Ascorbic acid[b]<br>Interferon[b] | 19 |
| 3 | 25/M | 32 | Prednisolone[b]<br>IVG,[b] splenectomy[a]<br>VCR,[a] VCR[b] | 8 |
| 4 | 21/F | 3 | Prednisolone,[b] IVG[a]<br>Splenectomy[a] | 3 |

*IVG, intravenous immunoglobulin (1–2 g/kg); VCR, vincristine (2 mg, as bolus injection).
[a]Response (>50 × 10 g/l after therapy).
[b]No response (platelet count <50 × 10 g/l after therapy).

initial forms of therapy or who relapse after splenectomy pose a significant clinical problem. This is reflected in the number of salvage therapies employed [1–3]. Recently, Andersen [4] reported excellent results of pulsed dexamethasone (DXM) in patients with resistant ITP. We describe here our initial experience of DXM in refractory ITP.

Four young (age 20–29 years) patients were treated with pulsed DXM for refractory ITP between June 1994–January 1996. The patients had received multiple therapies for symptomatic ITP, and all had been splenectomized 1–34 months before initiation of DXM pulses. All patients had symptomatic thrombocytopenia (platelet count, 3–19 × $10^9$/l) at the time of first DXM cycle. The basic characteristics of the patients and their previous treatments are shown in Table I.

The patients were treated with pulsed oral DXM (40 mg/day for d1–4, repeated after 4 weeks). Response to every DXM cycle was assessed by measuring platelet counts 1–3 weeks after each cycle and otherwise if bleeding symptoms occurred. A response was defined as a platelet count >50 × $10^9$/l during DXM therapy or within a month after the last DXM pulse (excluding values shortly after intravenous immunoglobulin, when used). The status of patients is as of March 31, 1996.

One patient (patient 1) responded after the first DXM cycle (platelet count, 175 × $10^9$/l), although the response was of short duration. Despite continuation to seven DXM cycles, she was severely thrombocytopenic and needed repeated intravenous immunoglobulin infusions and later azathioprine to maintain platelet counts at about 50 × $10^9$/l. Patient 2 responded slowly, and the platelet count was <50 × $10^9$/l after five cycles. This patient has now been off therapy for 16 months, with platelet counts of >50 × $10^9$/l.

Patients 3 and 4 were completely refractory to pulsed dexamethasone (two and four cycles, respectively). Patient 3 achieved unmaintained complete remission after interferon therapy. Patient 4 has now partially responded to vincristine therapy. In general, pulsed DXM was well-tolerated, with upper gastrointestinal symptoms predominating.

In this preliminary experience, pulsed DXM offered clinical benefits in 2 of 4 patients, with only one long-term unmaintained response. These observations seem to differ from experiences with similar therapy reported by Andersen [4]. In her series, all 10 patients with refractory ITP responded quickly. Complete unmaintained remission at 6 months after therapy was observed in all patients. In respect to number of previous therapies and platelet counts, the patients described by Andersen [4] seems to closely resemble that of our patients. Our observations, based on a very limited number of patients, suggest that clinical benefits of pulsed DXM may be only modest in patients with refractory ITP. This is supported also by recent observations from two small patient series [5,6].

Although disease-specific mortality in ITP is low (0–4%, reviewed by Schattner and Bussel [7]), these risks may be higher in patients with refractory ITP. Older age, history of previous bleedings, and concomitant thrombopathy are risk factors for fatal outcome [7]. In younger patients, bleeding symptoms, although usually not dangerous, may be severely distressing and lead to significant restriction of daily activities.

Numerous therapies have been tried in ITP patients unresponsive after corticosteroid treatments and splenectomy. These include azathioprine, vinca-alcaloids, cyclosporin, danazol, cyclophosphamide, and interferon. Limited information is available regarding comparative efficacy of these various therapeutic modalities. Therefore, therapeutic decisions in individual patients should be based on patient characteristics, including age and severity of bleeding symptoms, convenience, side-effects, and costs.

Pulsed DXM is an inexpensive and relatively well-tolerated regimen for the treatment of refractory ITP. Its efficacy may, however, not be as high as previously reported. More clinical experience is needed in this respect, with definition of characteristics predicting responsiveness.

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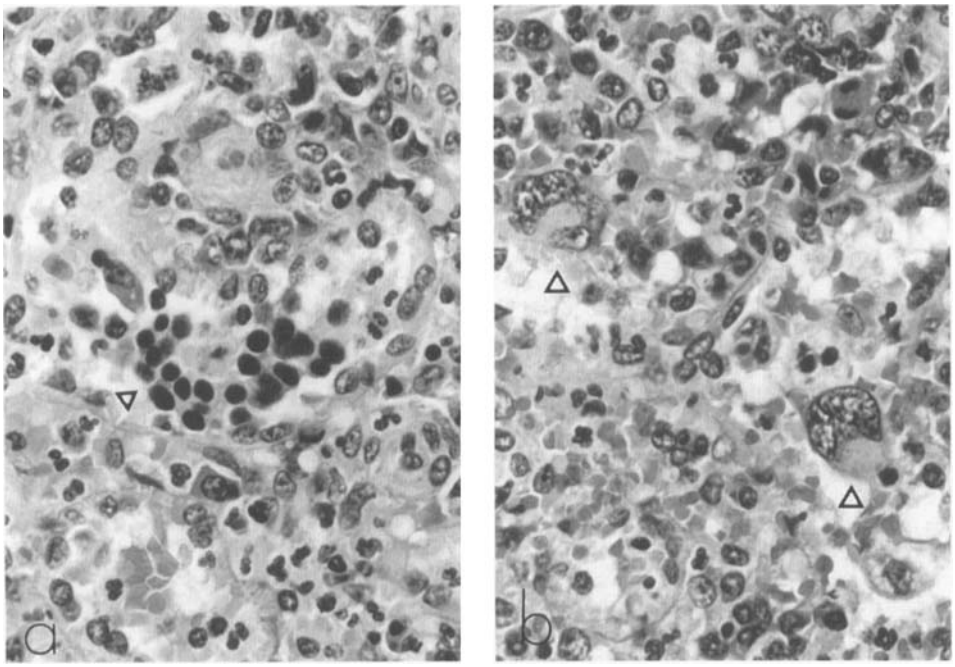

**Fig. 1. a: Red pulp. Many mature and immature granulocytes, and a colony of normoblasts (arrowhead). b: Red pulp. Two megakaryocytes (arrowheads).**

## Splenic Hematopoiesis After Granulocyte-Colony Stimulating Factor Therapy in a Lupus Patient

*To the Editor:* Extramedullary hematopoiesis after treatment with granulocyte-colony stimulating factor (G-CSF) has been reported three times in the literature [1–3]. A total of 4 patients had developed extramedullary hematopoiesis after either intermittent or continuous G-CSF administration. Two had hematopoiesis in the spleen, and 2 in the lymph nodes.

We now report on a fifth patient, a 46-year-old woman with long-standing lupus, whose spleen showed trilineage hematopoiesis after nine intermittent doses of G-CSF for treatment of pancytopenia over a 1-month period.

A 46-year-old Chinese woman with a 10-year history of SLE had been in stable condition until 3 weeks prior to hospitalization, when she developed a high fever which did not respond to antibiotics. A blood test revealed pancytopenia, (hemoglobin, 11 g/dl; white cell count, $1.7 \times 10^9$/l; and platelet count, $70 \times 10^9$/l), but marrow showed 60% cellularity with active and normal trilineage hematopoiesis. The cause of the fever was chest infection, as confirmed by X-ray.

She was initially treated with high-dose steroid and broad-spectrum antibiotics. When the platelet count deteriorated (to as low as $1 \times 10^9$/l) and the leukocyte count did not improve, she was given intravenous immunoglobulin at 2 g/kg over 5 days, and nine doses of intermittent G-CSF at 300 μg per daily dose over a period of 1 month. Two to three consecutive doses of G-CSF were given whenever the leukocyte count fell below $4.0 \times 10^9$/l.

Splenectomy was performed 2 days after the last dose of G-CSF. Two days postsplenectomy, the platelet count rose up $97 \times 10^9$/l. Two months later, hemoglobin was 13.2 g/dl, the leukocyte count was $8.4 \times 10^6$/l, and the platelet count was $351 \times 10^6$/l.

Grossly, the spleen weighed 170 g (normal range for Chinese female adults, 100–120 g). The outer surface was smooth and glistening, and the cut surface was congested. Microscopically, the spleen showed an intact architecture with expanded red pulp and diminished white pulp. In the red pulp, immature and mature granulocytes were frequently found. Occasional megakaryocytes and clusters of normoblasts were also identified (Fig. 1).

Extramedullary hematopoiesis in humans receiving G-CSF was first reported by Glasby and Golde [1] in 1992. A patient with idiopathic neutropenia who had been given daily G-CSF for 4 months developed splenomegaly. The resected spleen showed pronounced hematopoiesis. The authors also alluded to some other patients in their series having splenic hematopoiesis. In 1993, Litam et al. [2] reported on a patient with malignant lymphoma who developed splenomegaly after 56 intermittent doses of G-CSF. The splenectomy specimen showed patchy extramedullary hematopoiesis of all three lineages [2]. In 1994, Redmond et al. [3] described 2 patients with carcinoma of the breast who had received intermittent G-CSF in conjunction with chemotherapy. Extramedullary hematopoiesis was found in some resected lymph nodes. One patient had received 56, and the other 34, doses of G-CSF.

In our patient, splenic hematopoiesis was found after only nine intermittent doses of G-CSF over a 30-day period. The mildly enlarged spleen could have been due to hematopoiesis, which, as in most previous cases, was trilineage, although granulocytes were the predominant cells.

This case indicates that extramedullary hematopoiesis may be very common, if more organs such as lymph nodes and spleen become available for histological examination and that it may occur after very few doses of G-CSF treatment.

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